Please cancel claims 2 and 7.

In claim 17, line 1, after "method", please insert --of--.

REMARKS

Informal Matter

An election was made with traverse to prosecute the invention of claims 1-9, 16 and 17. This election is hereby affirmed.

The 35 U.S.C. §112 Rejection

Claims 2 and 7 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is traversed.

Claims 2 and 7 have been cancelled. Therefore, the rejection of claims 2 and 7 under 35 U.S.C. §112 is moot.

The 35 U.S.C. §102(e) Rejection

Claim 17 stands rejected under 35 U.S.C. §102(e) as being anticipated by **Bellgrau** et al. This rejection is traversed.

Bellgrau et al. teaches a method of suppressing T-lymphocyte-mediated rejection of transplanted tissue by implanting purified Fas ligand with pumps, wherein the diabetic rats are grafted with islet cells and implanted Fas ligand with a programmed pump

(see Example 1). In **Bellgrau**'s method, the donor organ tissue, i.e., islet cells, and Fas ligand are introduced to the recipients through different routes and at different times. In contrast, Applicants' claim 17 recites a method of decreasing rejection of a graft by perfusing donor organ tissue with Fas ligand first and then introducing the donor organ tissue to the recipient. That is, the graft and Fas ligand are introduced to the recipient through the same route and at the same time. Therefore, **Bellgrau** et al. does not teach each and every component of Applicants' claim 17 and, in fact, teaches away from the method of claim 17. Accordingly, Applicants request that the rejection of claim 17 under 35 U.S.C. §102(e) be withdrawn.

The 35 U.S.C. §103(a) Rejection

Claims 1-7 and 17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over **Bellgrau** et al. in view of **Süss** et al. Further, claims 1-7 and 17 stand rejected under 35 U.S.C. §103(a) as being unpatentable over **Bellgrau** et al. in view of **Schuler** et al. These rejections are respectfully traversed.

Bellgrau et al. teaches a method for treating T-lymphocyte-mediated rejection primary disease by introducing a cell which expresses the Fas ligand. **Bellgrau** et al. does not teach the

use of antigen presenting cells to induce systemic tolerance to an antigen. In addition, **Bellgrau** et al. teaches away from claim 17, as discussed above.

Süss et al. teaches that $CD8^+$ dendritic cells express Fas ligand and induces apoptosis of $CD4^+$. **Süss** et al. does not teach or suggest a method by using antigen presenting cells expressing Fas ligand to induce systemic tolerance to an antigen in an individual.

Schuler et al. is a review article that teaches that dendritic cells within thymic medulla are critical in inducing central tolerance (page 320, col. 2). **Schuler** et al. further cites Süss et al. as evidence that $CD8^+$ expressing dendritic cells express Fas ligand at high levels and kill $CD4^+$ T cells. No data are given in **Schuler** et al. demonstrating the method of inducing antigen-specific systemic tolerance by administering antigen presenting cells expressing Fas ligand and the antigen as claimed in the present invention.

The non-obviousness of the method of inducing antigen-specific T-cell tolerance by administering Fas ligand (FasL) bearing antigen presenting cells (APCs) is supported by Chen and Wilson, *Nature Biotechnology* 16: 1011-1012, 1998 (copy enclosed), which analyzes Applicant's method. As pointed out in Chen and Wilson, FasL is a potent inducer of apoptosis and has been actively pursued

as a therapeutic agent for conditions associated with excessive cell proliferation. However, the therapeutic value of FasL has been undermined by the recognition that FasL can both protect and damage self tissues. Because of these advantages and disadvantages of FasL, a method of disarming the immune system by administering FasL to reduce the T lymphocyte barrier to gene therapy has not been disclosed in the prior art. In the present invention, FasL is introduced to and expressed by the antigen presenting cells, wherein FasL induces apoptosis of T cells leading to antigen-specific T-cell tolerance. Dr. Wilson (the director of Institute for Human Gene Therapy and chair of the Department of Medicine and of Molecular and Cellular Engineering at University of Pennsylvania School of Medicine) noted that the method of inducing antigen-specific T-cell tolerance by administering FasL expressing antigen presenting cells is ingenious, wherein FasL kills only unwanted immune cells, not other self tissues (Chen and Wilson, page 1011, middle col.).

In view of the above arguments, Applicants respectfully submit that **Bellgrau** et al. in view of **Süss** et al., and further **Bellgrau** et al. in view of **Schuler** et al. do not render obvious claims 1-7 and 17. Accordingly the rejections of claims 1-7 and 17 under 35 U.S.C. §103(a) should be withdrawn.

This is intended to be a complete response to the Office Action mailed October 27, 1998. Applicants submit that the pending claims are in condition for allowance. If any issues remain, please telephone the attorney of record for immediate resolution.

Respectfully submitted,

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